AHRQ Healthcare Horizon Scanning System – Potential High-Impact Interventions Report

Priority Area 07: Diabetes Mellitus

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Statement of Funding and Purpose
This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHSA290-2010-00006-C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual topic profiles are developed for technologies and programs that appear to be close to diffusion into practice in the United States. Those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify interventions that experts deemed, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually and topics included may change depending on expert comments received on interventions issued for comment during the preceding 6 months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in horizon scanning, assessing the leads for topics, or providing opinions regarding potential impact of interventions.

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None of the individuals compiling this information has any affiliations or financial involvement that conflicts with the material presented in this report.

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Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor emerging technologies and innovations in health care and to create an inventory of interventions that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption, except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the Institute of Medicine and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is analyzing the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future use and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High-Impact Interventions report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to: effectivehealthcare@ahrq.hhs.gov.

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Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identification of new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 3 years out on the horizon and then to follow them up to 2 years after initial entry into the health care system. Since that implementation, review of more than 18,000 leads about potential topics has resulted in identification and tracking of about 2,000 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 550 topics are being actively tracked in the system.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice a year. Topics eligible for inclusion are those interventions expected to be within 0–3 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling information on topics and issuing topic drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 150 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest

(COIs). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the five to eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts' rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of "lower," "moderate," or "higher" within the high-impact-potential range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received and as the development status of the interventions changes, the list of topics designated as having potentially high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ's Effective Health Care Web site.

Results

The table below lists the four topics for which (1) preliminary phase III data for drugs, at least phase II or equivalent data for devices and procedures, or some human data for off-label uses or programs were available; (2) information was compiled before November 4, 2014, in this priority area; *and* (3) we received five to seven sets of comments from experts between January 1, 2014, and November 13, 2014. (Fifteen topics in this priority area were being tracked in the system as of November 4, 2014.) For this report, we aggregated related topics for summary and discussion (e.g., individual drugs into a class). We present three summaries on topics (indicated below by an asterisk) that emerged as having high-impact potential on the basis of experts' comments and assessment of potential impact.

The material on interventions in this Executive Summary and report is organized alphabetically by disease state and then by intervention. Readers are encouraged to read the detailed information on each intervention that follows the Executive Summary.

Priority Area 07: Diabetes

Topic	High-Impact Potential
1. * Artificial pancreas device system (MiniMed 350G with Enlite low-glucose suspend system) for treatment of diabetes requiring exogenous insulin	High
2. Degludec ultra-long-acting insulin (Tresiba) and degludec plus aspart (Ryzodeg) for treatment of type 1 or 2 diabetes	No high-impact potential at this time
3. * Fluocinolone acetonide implant (Iluvien) for treatment of diabetic macular edema	Lower end of the high-impact-potential range
4. * ITCA 650 (exenatide continuous subcutaneous delivery) for treatment of type 2 diabetes	Lower end of the high-impact-potential range

Discussion

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia (elevated blood sugar). Diabetes-associated hyperglycemia results from dysfunction in either insulin secretion or insulin action or both. Most diabetes mellitus cases are either type 1 diabetes mellitus (T1DM; 5% of cases) or type 2 diabetes mellitus (T2DM; ~95% of cases). The American Diabetes Association (ADA) reports that about 29.1 million children and adults in the United States have

diabetes mellitus, but only about 21 million have received a formal diagnosis. Furthermore, about 86 million people in the United States have prediabetes or are at risk of developing T2DM. ADA stated that clinicians diagnosed 1.7 million new cases of diabetes in U.S. people aged 20 years or older in 2012 (the most recent year for which statistics are available).

T1DM risk factors include family history of T1DM and presence of certain genetics, whereas T2DM risk factors include being overweight, having a body that primarily stores fat in the abdomen, having a family history of the disease, or having another form of diabetes mellitus such as prediabetes or gestational diabetes. Being African American, Hispanic, American Indian, or Asian American is also a risk factor for T2DM. According to the U.S. Centers for Disease Control and Prevention (CDC), diagnosed T2DM is seven times as prevalent in adults aged 65 years or older as in adults aged 20–44 years.

ADA states that T1DM is caused by destruction of the pancreatic beta cells, preventing secretion of insulin, and that this destruction is either immune mediated or idiopathic, with immune-mediated destruction accounting for the majority of cases. T1DM can occur at any age, but is most often diagnosed in children, adolescents, or young adults. Patients with T1DM require insulin therapy.

T2DM hyperglycemia is a result of insulin resistance or a diminished response to insulin. ADA states that patients with T2DM also often have a relative insulin deficiency and may have an insulin secretory defect in conjunction with insulin resistance.

Clinicians use one of three tests to diagnose diabetes mellitus: fasting plasma glucose test, oral glucose tolerance test, and casual plasma glucose level measurement. A fasting plasma glucose level of 126 mg/dL or more, an oral glucose tolerance test reading of 200 mg/dL or more, or a casual plasma glucose level of 200 mg/dL or more in conjunction with hyperglycemia symptoms all signal a diabetes diagnosis.

Additionally, a glycated hemoglobin (HbA_{1c}) test may be performed. This test indicates the patient's average blood sugar level for the previous 2 or 3 months, and an HbA_{1c} level of 6.5% or higher on two separate tests is considered to be diagnostic of diabetes. HbA_{1c} levels ranging from 5.7% to 6.4% indicate a diagnosis of prediabetes, with normal levels below 5.7%.

Treatment and management to prevent complications require patients to make a lifelong commitment to exercising regularly, maintaining a healthy weight, eating healthy foods, monitoring blood sugar, and, in some cases, taking insulin. The primary treatment goal is to maintain blood sugar levels as close to normal as possible to delay or prevent complications.

After diagnosis and disease-type classification, patients undergo evaluation to detect complications, review glycemic control challenges, and establish treatment goals and a treatment plan. Clinicians generally encourage patients to achieve an HbA_{1c} level of 7% or lower because this value has been shown to reduce diabetes-associated microvascular complications. However, targets are individualized according to clinician judgment about the optimal goal for a specific patient.

For T2DM, several self-administered, oral antidiabetes agents, alone or in combination, are generally tried as first-line therapy. These include biguanides, sulfonylureas, alpha-glucosidase inhibitors, insulin sensitizers, insulin secretagogues, and dipeptidyl peptidase-4 inhibitors. Many patients with T2DM do not meet treatment goals and require additional therapy with one of two types of injected antidiabetes agents: subcutaneous insulin or a glucagon-like peptide-1 (GLP-1) agonist. Insulin supplementation has become increasingly common with T2DM.

Most new treatments in development for diabetes focus on delaying disease onset in at-risk patients, improving diabetes management and treatment adherence, and for T1DM, developing options that prevent the body's autoimmune reaction against pancreatic islet cells or mimic the natural function of the pancreas to produce insulin.

Prior Potential High Impact Topic Not Eligible for Inclusion in This Report

- **Metabolic (bariatric) surgery for resolution of type 2 diabetes in mildly obese and nonobese patients:** Metabolic surgery (i.e., gastric bypass, lap banding, sleeve gastrectomy) has become a therapy used to induce T2DM remission in patients who have been unable to achieve adequate control with first- or second-line therapy. Although initially used for patients with T2DM with body mass index (BMI) >35 kg/m^2 (with comorbidities) or with BMI >40 kg/m^2, this approach has been used more recently for patients with BMI <35 kg/m^2 as well. Some clinical researchers believe that BMI-based criteria for bariatric surgery are not adequate for determining eligibility in patients with diabetes. Therefore, most obesity or bariatric surgery professional societies have added the term "metabolic" to their organization names. Guidelines specify that bariatric surgery is indicated for individuals who are morbidly obese (i.e., BMI >40 kg/m^2) or individuals with a BMI >35 kg/m^2 and an associated comorbidity. One such qualifying comorbidity is diabetes, which is highly correlated with obesity, and outcomes showing resolution of T2DM in patients who have undergone bariatric surgery has generated interest in the potential of bariatric surgery to treat T2DM in less-obese patients (i.e., BMI <35 kg/m^2). This topic was designated in the June 2014 Potential High-Impact Interventions report (and prior reports) as having potential for high impact; however, the comments on this topic were received more than 1 year ago, and per protocol, eligibility for consideration requires comments having been received within the past 12 months. We continue tracking this topic, and will obtain new comments from experts for consideration in the next Potential High-Impact Interventions report.

Prior Topic Deemed High Impact but No Longer High Impact

- **Degludec ultra-long-acting insulin (Tresiba) and degludec plus aspart (Ryzodeg) for treatment of type 1 or 2 diabetes:** Degludec is an ultra-long-acting basal insulin analog in development for treating T1DM and T2DM in patients requiring insulin therapy. Insulin degludec/insulin aspart is a soluble formulation of insulin degludec (70%) combined with insulin aspart (30%) (NovoLog®), a fast-acting mealtime insulin analogue. Novo Nordisk a/s, Bagsvaerd, Denmark, is developing insulin degludec and insulin degludec/insulin aspart. According to the company, the U.S. Food and Drug Administration (FDA) has requested additional cardiovascular data from a dedicated cardiovascular outcomes trial. A global cardiovascular outcomes trial is under way comparing insulin degludec to insulin glargine in patients with T2DM at high risk of cardiovascular events. Prespecified interim analysis of major adverse cardiovascular events is anticipated by mid-2015. In light of FDA's decision, we will continue to track this topic in the horizon scanning system, although for this report it was considered as not having high-impact potential at this time.

Eligible Topics Deemed High Impact

Artificial Pancreas Device Systems (MiniMed 530G with Enlite Low-Glucose Suspend System) for Treatment of Diabetes

- **Key Facts:** An artificial pancreas device system (APDS) consists of an external or implantable insulin pump, real-time continuous glucose monitor, and a small computing device with software and algorithms to detect glucose levels and coordinate appropriate insulin delivery. Many believe that the APDS will be the ideal management strategy for

patients with diabetes who require intensive insulin therapy. Researchers and manufacturers are developing two types of systems: reactive and predictive low-glucose suspend systems. In reactive systems, patients or clinicians set a blood glucose threshold, and the pump automatically shuts off when that reading is reached. In predictive systems, the monitor uses control algorithms that predict when the patient's blood glucose is projected to decrease to a dangerously low level. Although many proof-of-concept studies of closed-loop systems (CLSs) have been performed and all the necessary component parts of a CLS exist, a truly portable CLS for routine use is likely several years from realization. This is because major advances in sensor technologies and artificial pancreas software algorithms are needed, as is a developer that integrates the disparate components into a single CLS.

The JDRF (formerly the Juvenile Diabetes Research Foundation) has committed significant resources to developing a system, and several are in pilot studies. In November 2012, FDA issued guidance for developers titled, "The Content of Investigational Device Exemption (IDE) and Premarket Approval (PMA) Applications for Artificial Pancreas Device Systems" to guide trial conduct and regulatory submissions.

The MiniMed 530G with Enlite® sensor (Medtronic, Inc., Minneapolis, MN) is the first step toward a commercially available APDS. FDA approved the MiniMed 530G system for marketing in September 2013. The system uses threshold-suspend automation, a feature intended to automatically stop insulin delivery (for up to 2 hours) when sensor glucose values reach a preset level and when the patient does not respond to the threshold suspend alarm. The indication is "for use by people with diabetes ages 16 and older, requiring insulin as well as for the continuous monitoring and trending of glucose levels in the fluid under the skin." This system is the first to be approved under FDA's new product classification, "OZO: Artificial Pancreas Device System, Threshold Suspend."

Estimates list the retail price at $7,350, with insured patients reporting copayments from $5 to up to 50% of costs. Medtronic introduced the Path2System Program to aid adoption by existing pump users. According to the company, patients using the Paradigm® Revel™ Insulin Pump and Continuous Glucose Monitoring (CGM) system with a valid warranty can obtain the new MiniMed 530G system for $399 plus the varying cost of the Enlite starter kit. Patients' out-of-pocket costs for CGM vary according to their health plan coverage. The Path2System includes the MiniMed 530G insulin pump; Enlite training packet; MiniLink transmitter, charger and test plug; and Enlite Starter Kit. For patients currently using a Medtronic CGM, the estimated cost to obtain the MiniMed 530G System and use it for a year would be about $7,975. Many third-party payers cover the system according to its labeled indication for patients who meet criteria for an external insulin pump.

- **Key Expert Comments:** Overall, experts agreed on the need for systems that help patients achieve adequate glucose control. Most experts commenting on this intervention opined that it has the potential to improve patient health outcomes by reducing hypoglycemic episodes. Several experts commented that the intervention would significantly improve health outcomes in patients with hypoglycemia unawareness. Most experts commented that this intervention represents an important step towards a true APDS. However, experts cited the inability to address hyperglycemic episodes as a limiting factor. Experts generally agreed that both patients and clinicians would adopt this intervention. However, some experts cited cost, insurance coverage, and device training to be potential barriers to acceptance.
- **High-Impact Potential:** High

Fluocinolone Acetonide Implant (Iluvien) for Treatment of Diabetic Macular Edema

- **Key Facts:** According to the World Health Organization, people with diabetes who do not receive appropriate eye care have a 20% to 30% chance of developing clinically significant diabetic macular edema (DME). This condition leads to moderate or total vision loss over time. The main treatment for DME was macular focal/grid laser photocoagulation until August 2012, when FDA approved another therapy, ranibizumab injection (Lucentis®), a once-monthly eye injection. Iluvien® (Alimera Sciences, Inc., Alpharetta, GA) is a tiny tube containing 190 mcg of fluocinolone acetonide that is injected once into the back of the eye with a 25-gauge needle in a single, in-office procedure. Over 3 years, the tube purportedly releases a constant, low flow of medication; thus, it does not require monthly injections as does Lucentis. The exact mechanism of action is unknown, but fluocinolone acetonide is thought to work through its combined vasoconstrictive, anti-inflammatory, and antipruritic activity, which is inherent to corticosteroids such as fluocinolone. In September 2014, FDA approved Iluvien® for treating DME in patients "who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure." The drug-device combination is likely to compete with ranibizumab and aflibercept (Eylea®) injections. Fluocinolone acetonide's history of regulatory rejections and potential risk of increasing intraocular pressure might dissuade physicians from embracing fluocinolone acetonide implants to treat DME until a larger body of evidence becomes available.
- **Key Expert Comments:** Overall, experts commenting on this intervention opined that this intervention could offer a long-lasting, single-procedure pharmacotherapy as an alternative to laser photocoagulation or monthly injections of ranibizumab for treating DME. However, experts were unsure whether this intervention would be as effective as monthly injections of ranibizumab, because of the lack of comparative clinical trials. Experts also expressed concerns regarding potential adverse events, including cataracts and increased intraocular pressure. Experts generally agreed that this intervention has the potential to be widely accepted by patients and clinicians. However, several experts commented that the risk of adverse events could affect patient and clinician adoption, although other experts opined that patients might be willing to accept this risk if it prevents vision loss. Experts noted that the intervention has the potential to reduce per-patient costs of treatment. However, some experts noted that cost savings could be nullified if patients need to be treated for device-related adverse events.
- **High-Impact Potential:** Lower end of the high-impact-potential range

ITCA 650 (Exenatide Continuous Subcutaneous Delivery) for Treatment of Type 2 Diabetes

- **Key Facts:** ITCA 650 (Intarcia Therapeutics, Inc., Hayward, CA), is extended-release exenatide for injection (Bydureon™, AstraZeneca, London, UK). ITCA 650 is a proprietary formulation of exenatide delivered through a proprietary system consisting of a "matchstick-sized osmotic pump" that is inserted subcutaneously into the patient's arm or abdomen to purportedly deliver a slow and consistent flow of medication. Exenatide, a GLP-1 receptor agonist that has been available since 2005, is an incretin mimetic that patients inject twice daily, before meals. The delivery system is intended to be used for long-term subcutaneous delivery at a controlled rate for treating T2DM, and ITCA 650 is reported to remain stable at body temperature for delivery up to 12 months, based on data presented thus far. The outpatient implantation procedure is performed by a physician and takes about 5 minutes. The company reported in October 2014 that two phase III trials (FREEDOM 1 and FREEDOM 1 high baseline) had been successfully completed and two are ongoing. FREEDOM 1 reportedly met all endpoints for HbA_{1c} and weight reductions, and the percentage of patients treated to goal. Significant HbA_{1c} reductions observed over the 39 weeks of the study ranged from a "mean of 1.4% to 1.7%" across the majority of patients. The highest reductions were observed in patients also receiving metformin. Patients with a baseline HbA_{1c} "above 8.5%" had mean reductions "up to 2.1%." Two dosages were used and both (40 mcg/day and 60 mcg/day mini-pumps) reportedly showed statistically significant results versus control group and were well tolerated. The FREEDOM-1 high baseline (HBL) study showed consistently maintained HbA_{1c} level reductions of "3.4%" by 39 weeks from a mean starting baseline of "10.8%." Most patients had had poorly controlled T2DM despite being on multi-drug therapy. Use of ITCA 650 added to therapy reportedly enabled 25% of patients to reach an HbA_{1c} goal of less than 7% at week 39. (We believe the results for HbA1c that the company stated as percent changes should instead be expressed as percentage points.) Intarcia stated that it expects to file for regulatory approval of ITCA 650 in the United States in early 2016. No information is available about anticipated costs.
- **Key Expert Comments:** Experts generally agreed on the need for effective T2DM treatments, citing patient adherence issues and the lack of efficacy of available treatments. They agreed on the potential of this intervention to reduce the burden of frequent injections and to provide consistent, effective treatment. However, several experts expressed concerns about the potential for side effects with GLP-1 receptor agonists, including pancreatitis and pancreatic cancer; although a causal link has not been established. Most experts opined that both clinicians and patients would be likely to accept this intervention, especially if they are achieving adequate glucose control with available GLP-1 receptor agonists. However, one expert commented that patients may not be willing to have the device implanted if side effects persist during the implantation period. Experts generally agreed that the initial cost of the device would likely be offset by the long-term savings from reduced disease-related complications, if proved effective.
- **High-Impact Potential:** Lower end of the high-impact-potential range

Diabetes Mellitus Interventions

Artificial Pancreas Device Systems for Treatment of Diabetes (MiniMed 530G with Enlite Low-Glucose Suspend System)

Unmet need: Fluctuating glucose levels make diabetes management and control difficult, often requiring adjustments to insulin dosage in diabetic patients requiring insulin. Researchers estimate that two-thirds of diabetic patients do not achieve adequate glycemic control using traditional glucose meters and continuous glucose monitors (CGMs) to guide insulin treatment. This increases the risk of secondary complications, including cardiovascular disease, retinopathy, nephropathy, and neuropathy. Therefore, a medical need exists for systems that improve insulin delivery methods and glycemic control.[1-3]

The artificial pancreas device system (APDS) is intended to provide a complete system, known as a closed-loop system, to mimic pancreatic activity by combining several technologies—a glucose monitoring device, an external or implantable insulin pump, and a glucose sensor with advanced-algorithm software—to optimize diabetes management.[4]

Intervention: Fully automated APDSs are several years away from availability, but systems incorporating some of the functionality of a fully automated APDS are starting to emerge in the U.S. market. One class of technology being developed is a system that continuously monitors glucose levels and automatically adjusts insulin delivery in response to those levels.[5] One such system is the MiniMed 530G System, which integrates a low-glucose suspend (LGS) or threshold suspend algorithm intended to reduce the severity and duration of hypoglycemic events by automatically suspending insulin administration when a person's glucose levels drop below a preset level.[6]

An APDS consists of an external or implantable insulin pump, a system that can monitor blood glucose levels in real time, and a small computing device that uses an algorithm to determine insulin dosage delivery.[4] The computerized algorithm is designed to deliver appropriate doses of insulin from the insulin pump.[7]

In a November 2012 guidance document on APDS development,[5] the U.S. Food and Drug Administration (FDA) defined the components of APDSs as follows, stating that they are categorized as Class III devices:[8]

- Glucose monitoring devices—a CGM and blood glucose device used for calibrating the CGM (as applicable) and checking sensor performance as needed plus associated reagents/test strips
- APDS control algorithm
- Infusion pump—a fluid infusion set for the complete fluid pathway from the drug reservoir or fluid source container (e.g., bag, cassette, vial, syringe), infusion set, extension sets, filters and valves, clamps, up through the patient connection
- Components and accessories (e.g., power cord, wireless controller)

This definition includes a closed-loop system as well as first-generation systems LGS systems. For an implantable APDS, an endocrinologist administers local anesthesia and surgically implants the pump and glucose monitor subcutaneously on opposite sides of the abdomen. The insulin reservoir is placed beneath the skin and is refilled every 2–3 months via transcutaneous injection.[4] In LGS APDSs, insulin delivery automatically shuts off when blood glucose levels drop below a preset threshold indicating hypoglycemia (reactive), or the monitor uses control algorithms to predict and prevent potential hypoglycemic events (predictive).[5]

The MiniMed 530G with Enlite® sensor is the first LGS system on the market. It is intended for patients with diabetes who need exogenous insulin and wish to use a pump with a CGM system. The system is considered a first-generation APDS incorporating a reactive LGS algorithm. The

system uses threshold suspend automation to automatically stop insulin delivery (for up to 2 hours) when sensor glucose values reach a preset level and when the patient does not respond to the threshold suspend alarm.[9] According to the manufacturer, threshold suspend may be set between 60 and 90 mg/dL, and can deliver a manual bolus of up to 25 units of insulin.[6]

The MiniMed 530G system consists of the following:[10]

- An insulin pump with CGM
- The new Enlite continuous glucose sensor (with Enlite Serter)
- The new Contour® Next Link wireless blood glucose meter (Bayer Diabetes Care, Tarrytown, NY)

Clinicians and patients can use Medtronic's CareLink® Pro Therapy Software with the MiniMed 530G to monitor blood glucose levels and manage diabetes care.[10]

Medtronic reports that its Enlite sensor can be worn for 6 days, is 69% smaller than the company's previous-generation sensor, and offers a 31% improvement in overall accuracy compared with the previous model. According to the company, "the new Enlite Serter provides a simpler sensor insertion process with a hidden-introducer needle."[9]

The MiniMed 530G system uses the same calibration algorithm and threshold suspend software used in Medtronic's Veo™ insulin pump, which was developed earlier and is sold in Europe.[11] Like the MiniMed 530 G system, the LGS feature of the Veo insulin pump system was designed to reduce the severity and duration of hypoglycemia. Patients may use the pump with or without CGM sensors, and CGM-augmented Veo pump users may turn the LGS feature on or off.[12]

Clinical trials: Many APDS proof-of-concept trials are ongoing in the United States and internationally. Much of the research is supported by JDRF, formerly known as the Juvenile Diabetes Research Foundation.[13] In June 2014, Russell and colleagues reported outcomes from 5-day, random-order, crossover studies assessing the safety and efficacy of a "bionic" pancreas system in 20 adults and 32 adolescents with type 1 diabetes (T1DM). The authors reported a mean plasma glucose level reached over 5 days of a bionic-pancreas period of 138 mg/dL (7.7 mmol/liter), and a mean percentage of time with a low glucose level (<70 mg/dL [3.9 mmol/liter]) of 4.8%. After the bionic pancreas adapted for 1 day, the mean (±SD) glucose level shown from continuous glucose monitoring was lower than the mean level observed during the control period (133±13 vs. 159±30 mg/dL [7.4±0.7 vs. 8.8±1.7 mmol/liter], $p<0.001$). Among adolescents, authors reported that the mean plasma glucose level was also lower during use of the bionic-pancreas period than during the control period (138±18 vs. 157±27 mg/dL [7.7±1.0 vs. 8.7±1.5 mmol/liter], $p=0.004$). On average, fewer interventions were required for hypoglycemic episodes during the bionic-pancreas period than during the control period (1 per 1.6 days vs. 1 per 0.8 days, $p<0.001$).[14]

In September 2013, Ly and colleagues reported outcomes from a study assessing the safety and efficacy of an LGS system in 95 patients with T1DM. The authors reported[15] that 49 patients were assigned to pump-only therapy and 46 were assigned to the LGS group. The mean (SD) age was 18.6 (11.8) years and diabetes duration was 11.0 (8.9) years. Patients had been on pump therapy for a mean 4.1 (3.4) years. After 6 months of treatment, the hypoglycemic event rates in the pump-only group decreased from 28 to 16 and in the LGS group decreased from 175 to 35. The adjusted incidence rate per 100 patient-months was 34.2 (95% confidence interval [CI], 22.0 to 53.3) for the pump-only group and 9.5 (95% CI, 5.2 to 17.4) for the LGS group. The reported incidence-rate ratio was 3.6 (95% CI, 1.7 to 7.5; $p<0.001$). Researchers observed no change in glycated hemoglobin (HbA_{1c}) in either group. No episodes of diabetic ketoacidosis or hyperglycemia with ketosis were reported.

In July 2013, Bergenstal and colleagues published results from a pivotal, in-home, open-label, randomized control trial assessing the safety and efficacy of an LGS in 247 patients with T1DM.

The authors reported that using the threshold-suspend feature significantly reduced the area under the curve (AUC) for nocturnal hypoglycemia, the weekly rate of nighttime hypoglycemic events, and the percentage of nighttime spent with sensor glucose values in the hypoglycemic range. Further, these reductions in hypoglycemia measures with the threshold-suspend feature were observed for the full 24 hours. The outcome of lower exposure to hypoglycemia persisted in patient subgroups stratified according to age, diabetes duration, and HbA_{1c} levels at randomization and was achieved without significant changes in HbA_{1c}, severe hypoglycemic events, ketosis, or diabetic ketoacidosis. The authors concluded that the fact that "no significant between-group differences [were seen] in the number of study visits, insulin use, sensor wear and calibrations, or number of blood glucose determinations indicated that the reduction in hypoglycemia was due to the threshold-suspend feature itself."[16]

Manufacturer and regulatory status: The separate components that comprise an APDS have had marketing approval for some time.[7] FDA has issued a guidance document for the systems, intended to facilitate the clinical development of a fully CLS.[17,18] In November 2012, FDA published guidelines, "The Content of Investigational Device Exemption (IDE) and Premarket Approval (PMA) Applications for Artificial Pancreas Device Systems," to inform the sponsors of APDS IDE studies on how to support a PMA for "single patient use in the home environment."[8] In August 2013, FDA finalized the guidance and added it to resources about APDS research and development on its Web site.[19]

In June 2012, Medtronic submitted to FDA the final component of a modular PMA submission for the MiniMed 530G, supported in part by the ASPIRE in-clinic trial results.[20] Medtronic had initially promoted CGM integration by developing the MiniMed Paradigm Veo and had received FDA approval in late 2011 to begin the ASPIRE trial to evaluate a LGS APDS in the United States.[7,21] The ASPIRE clinical trial was designed to evaluate the safety and efficacy of the systems in a home setting.[21]

According to the company's FDA submission, "A similar insulin pump system containing the threshold suspend tool received a CE [Conformité Européene] mark under the name, Paradigm Real Time Veo System, and was commercialized in the European Economic Community in May 2010."[11] The Summary of Safety and Effectiveness Data for the MiniMed 530G states the following:[11]

> The effectiveness of the Threshold Suspend tool in correctly suspending insulin delivery at the set threshold was examined using the Sof-Sensor and the Medtronic Veo insulin pump. Though this system is not identical to the 530G system, this data can be extrapolated to support the safety and effectiveness of the 530G system for the following reasons. The software for the Threshold Suspend tool is the same for the Veo pump and the 530G System. Though the Medtronic Sof-Sensor and the Enlite sensor are not identical, they operate using similar principles and fundamental scientific technology.

FDA approved the MiniMed 530G with Enlite system for marketing in September 2013. The indication is "for use by people with diabetes ages 16 and older, requiring insulin as well as for the continuous monitoring and trending of glucose levels in the fluid under the skin."[9] The MiniMed 530G is the first system approved under FDA's new product classification, "OZO: Artificial Pancreas Device System, Threshold Suspend."

In accordance with FDA approval, Medtronic will conduct a postapproval study that will include children aged 2 years or older. A company press release further stated: "As a condition of approval, in addition to the post-approval study, Medtronic will engage in direct patient follow up and will make certain manufacturing accommodations. These commitments are consistent with the product approval by the FDA and an accompanying warning letter issued to Medtronic on Sept. 19,

2013." Medtronic stated in a November 2014 correspondence letter that it had addressed all observations noted in the warning letter, and that FDA was verifying its actions.[6,9]

At least three companies are pursuing APDSs.[22] Medtronic and another company, Tandem Diabetes Care, Inc., San Diego, CA, have formed a partnership with JDRF to advance technologies toward achieving a fully automated monitor/pump combination.[23] Animas Corp., a unit of Johnson & Johnson, New Brunswick, NJ, and DexCom, Inc., San Diego, CA, have collaborated to develop the Animas Vibe™ combined insulin pump and CGM, which received the CE mark in June 2011, allowing marketing in Europe. It has also been released in the United Kingdom.[21] In December 2014, Animas announced FDA approval of the Vibe system indicated for "detecting trends and tracking patterns in persons (age 18 and older) with diabetes."[24] It is the second available CGM-enabled insulin pump in the United States; however, it does not possess a threshold suspend or LGS feature as does the MiniMed 530G device.[25,26] The next generation of Medtronic APDS is the predictive type that suspends insulin delivery when the system predicts hypoglycemia in the patient.[27] Another device in the early stages of development consists of a bihormonal control system including both an insulin and glucagon pump combined with CGM, also known as a "bionic" pancreas.[14]

Diffusion and cost: The most appropriate patients for the technology are considered to be those with T1DM who frequently experience hypoglycemia, are highly motivated to achieve control, and are able to use an insulin pump.[28,29] Among suitable candidates, patients who have trouble maintaining normal nocturnal glycemia are expected to especially want to adopt use of an APDS.[30] Diffusion may take place at diabetes centers of excellence because of the level of expertise and comprehensive training required for using and monitoring device function.[31] However, if the APDS effectively slows disease progression, the device might become more widely available as the most desirable method of diabetes management in patients who require daily insulin.[3,32] Diffusion of the Medtronic MiniMed 530G began in late 2013. According to November 2014 correspondence, the manufacturer estimates that more than 53,000 MiniMed devices have been sold in the United States and more than 170,000 worldwide.[6]

For a patient not currently using a Medtronic pump or CGM, the estimated cost to obtain the MiniMed 530G System and use it for a year would be $14,550.[33-36] Medtronic introduced a program to aid adoption called the Path2System Program.[37] This enables patients who already have an "existing, in-warranty Paradigm® Revel™ Insulin Pump and Continuous Glucose Monitoring" to order MiniMed 530G with Enlite for $399 plus the varying cost of the Enlite starter kit. The Path2System includes the MiniMed 530G insulin pump; Enlite training packet; MiniLink transmitter, charger, and test plug; and Enlite Starter Kit. For patients currently using a Medtronic CGM, the estimated cost to obtain the MiniMed 530G System and use it for a year would be about $7,975. The Path2System includes the pump; Enlite training packet; data transmitter, charger, and test plug; and the Enlite Starter Kit. Medtronic states that patients should expect a wait of 90 days after applying for the program because of high demand.[37] The anticipated retail price for MiniMed 530G was $7,350 for those ineligible for the Path2System Program; insured patients reportedly typically pay $500 to $1,200 out of pocket, depending on their insurance copayments.[38] The company advises that patients' out-of-pocket costs for CGM vary according to their health plan coverage.

Animas anticipates a January 2015 launch of the Vibe system at a reported total cost of about $8,448.[25,39] The company reportedly has plans to offer a device upgrade program.[39]

Although a true APDS may raise the cost over that of standard CGM and insulin pumps, a study funded by JDRF projected that the technology could reduce diabetes-related expenses by slowing disease progression.[3,32,40] Total estimated costs of diagnosed diabetes in the United States were $245 billion in 2012, and an additional $69 billion was attributed to reduced productivity.[40]

The U.S. Centers for Medicare & Medicaid Services (CMS) does not have a coverage policy for use of this technology. We searched 13 private, representative third-party payers to identify whether they have policies that mention the MiniMed 530G device. We found five policies indicating that the following payers provide coverage: Aetna,[41] Blue Cross Blue Shield (BCBS) of Alabama,[42] CIGNA,[43] Excellus BCBS,[44] and Humana.[45] These payers typically provide coverage when certain eligibility criteria are met, including the labeled indication criteria. Several other payers, such as BCBS Massachusetts, BCBS North Carolina, HealthNet, Medica, Regence, and United HealthCare, have policies stating they do not provide coverage; they consider the device to be investigational at this time.

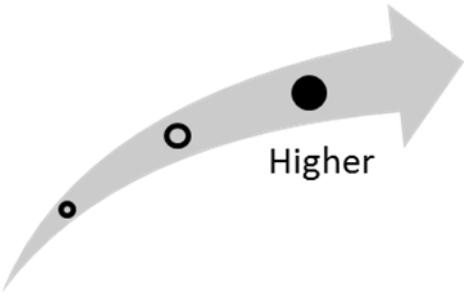
As the first system approved under FDA's new "Artificial Pancreas Device System, Threshold Suspend" product classification, the MiniMed 530G system might warrant a new CMS reimbursement category. Medtronic has reportedly applied for a new CMS code for the system, which is currently covered by existing CMS codes for insulin pumps and CGM.[46]

Clinical Pathway at Point of This Intervention

Upon receiving a diagnosis of diabetes, patients undergo medical evaluation to classify the disease type, detect any complications, review glycemic control challenges, and establish a treatment plan (depending on diabetes type and other medical factors). Part of this plan is establishing target HbA_{1c} goals. HbA_{1c} is a measure of the average amount of glucose in a patient's blood over a 2- or 3-month period, based on a single blood draw.

Patients with T1DM require insulin therapy. For type 2 diabetes mellitus (T2DM), one or more self-administered oral antidiabetes agents taken alone or in combination are generally tried as first-line therapy. Some patients with T2DM also need insulin therapy.[47] Clinicians encourage patients to achieve an HbA_{1c} level of about 7% or slightly lower, depending on the patient. This value has been shown to reduce some secondary complications associated with T1DM and T2DM. Patients and their diabetes care teams work to adjust insulin dosages using feedback from a blood glucose monitor.[7]

Figure 1. Overall high-impact potential: artificial pancreas device system (MiniMed 350G Low Glucose Suspend System) for treatment of diabetes requiring exogenous insulin



Overall, experts commenting on this intervention opined that it has the potential to improve health outcomes, especially in patients with hypoglycemia unawareness, by reducing hypoglycemic episodes. However, experts commented that the device's potential to improve patient health is limited by its inability to address hyperglycemic episodes. Most experts commented that this intervention represents an important step towards a true APDS. Experts generally agreed on the potential for widespread clinician and patient acceptance. However, some experts cited cost, insurance coverage, and device training to be potential barriers to acceptance. Most experts agreed that this intervention is not likely to affect health disparities. However, some experts commented that patients without health insurance may not be able to afford the out-of-pocket costs of the

device. Based on this input, our overall assessment is that this intervention is in the higher end of the high-impact-potential range.

Results and Discussion

Six experts, with clinical, research, health systems, and health administration backgrounds, provided perspectives on the MiniMed 530G with Enlite.[48-53] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: A significant need exists for interventions that continuously monitor blood glucose and automatically adjust insulin delivery in patients with diabetes who require exogenous insulin, noted the experts. They commented that this intervention has the potential to improve patient health outcomes by reducing hypoglycemic episodes. One clinical expert deemed the intervention to be advantageous because it can accurately predict hypoglycemia. The expert commented, "These features will benefit the treatment of type 1 and type 2 diabetes, as well as prevent morbidity in patients with hypoglycemia unawareness, a potentially deadly consequence of repeated hypoglycemic episodes associated with insulin therapy."[53] Some experts expressed concerns over the intervention's inability to respond to hyperglycemic episodes. One expert representing a research perspective opined, "The device under question will potentially minimize hypoglycemic events, which in and of itself is highly beneficial. When we have a system that can minimize hyperglycemic events, which are key factors for severe diabetic complications, then we will have made a huge step forward...."[52]

Acceptance and adoption: Experts noted that both patients and physicians would widely accept this intervention because of the benefits of increased glycemic control. One expert representing a health systems perspective opined, "I suspect there will be wide acceptance of this technology based on its clinical benefits and patient's ease of use post the learning period. This wide acceptance is predicated on the confidence of the clinicians regarding the accuracy of the technology to prevent hypoglycemia and respective complications."[49] Experts commenting on this intervention listed training and reimbursement to be potential barriers to acceptance for patients. However, one expert representing a research perspective opined that patients familiar with insulin pump use would easily grasp the concepts of device use.[51]

Health care delivery infrastructure and patient management: Most experts listed the health care professional training to be the largest potential disruption to health care delivery infrastructure. One expert representing a clinical perspective opined that sophisticated training would be required that would not likely be provided at a primary care clinic.[53] However, one expert representing a research perspective opined that this intervention would not likely affect medical centers familiar with insulin pump therapy. The expert commented, "Facilities that currently offer pump therapy programs already have in place multidisciplinary teams that would care for these patients… patients experienced in pump use would readily grasp concepts of device use."[51]

Most experts generally agreed that this intervention has a minimal potential to disrupt patient health management after the initial patient and clinician training phase is completed. One expert representing a health systems perspective anticipated a reduction in other medical services, including emergency room visits, intensive care services, and physician services.[49]

Health disparities: Most experts agreed that this intervention is not likely to impact health disparities. Some experts commented that patients without health insurance may not be able to afford the out-of-pocket costs of the device. However, one expert representing a research perspective opined, "Currently, pump users are highly educated, motivated patients with financial means to afford out-of-pocket expenses related to pump use."[51]

ITCA 650 (Exenatide Continuous Subcutaneous Delivery) for Treatment of Type 2 Diabetes

Unmet need: Despite the availability of oral antidiabetes drugs, many patients with T2DM do not meet treatment goals and require additional therapy with one of two types of injected antidiabetic agents: subcutaneous insulin or a glucagon-like peptide 1 (GLP-1) receptor agonist, also called an incretin mimetic.[54] Incretin mimetics have become standard treatments to improve glycemic control.[47] However, the GLP-1 receptor agonists approved by FDA—exenatide (Byetta®), liraglutide (Victoza®), and exenatide long-acting release (Bydureon™)—require twice-daily, once-daily, or once-weekly dosing, respectively, by subcutaneous injection.[55,56] More convenient dosing could potentially improve adherence to treatment recommendations and patient outcomes. ITCA 650 is in development and involves use of the GLP-1 receptor agonist exenatide, delivered through an implantable device providing a steady dose for up to 12 months.[57]

Intervention: ITCA 650 is a matchstick-sized, implantable device that is intended to deliver a steady dose of an incretin mimetic, exenatide, using a proprietary delivery system (Duros® technology). Exenatide, which has been available since 2005, is an incretin mimetic that patients inject twice daily, before meals. The new Duros delivery system is intended to deliver the drug subcutaneously, at a controlled rate over the long term. It has been used commercially since 2000 in a leuprolide acetate implant (Viadur®) for treating advanced prostate cancer.[58] The system is a miniature osmotic pump that essentially functions as a syringe.[58] Within a tubular titanium shell, the system contains a drug reservoir and an osmotic agent separated by a piston. Adjacent to the osmotic agent is a semipermeable membrane. The osmotic agent steadily draws water from the body across the membrane, which exerts pressure on the piston, forcing a steady flow of drug out of a small pore or diffusion moderator on the opposite side of the pump. Studies have demonstrated that the formulation of exenatide used in ITCA 650 is stable within the Duros pump for at least 1 year at body temperature, potentially allowing once-yearly system implantation.[59]

A physician or physician assistant inserts ITCA 650 into the patient's arm or abdomen during an outpatient procedure that takes about 5–10 minutes.[57] Clinicians can remove or replace the device in a similarly short procedure. The version of ITCA 650 that will be used in phase III clinical trials is intended to deliver a dose of 60 mcg of exenatide per day.[60]

Clinical trials: In March 2013, ITCA 650's developer announced enrolling the first patients in its phase III FREEDOM clinical program, which is expected to include more than 4,000 patients at 500 clinical trial sites in more than 30 countries. The studies will include a broad range of patients whose diabetes is uncontrolled by oral antidiabetes medications including metformin and metformin-based combinations.[61]

In October 2014, the company announced study results from two phase III trials in the FREEDOM program (FREEDOM-1 and FREEDOM-1 High Baseline [HBL]). A company press release included results from the completed FREEDOM-1 trial.[62] The company reported that investigators observed significant HbA_{1c} reductions over the 39 weeks (mean of "1.4% to 1.7%" across most patients). The highest reductions were seen in patients taking background metformin. Patients who had HbA_{1c} levels "above 8.5%" had statistically significant "mean reductions up to 2.1%" at both doses tested (40 mcg/day and 60 mcg/day mini-pumps). The company also reported preliminary results from the open-label FREEDOM-1 HBL trial:[62] Investigators observed sustained HbA_{1c} level reductions at 39 weeks of "3.4%" (mean) from baseline of "10.8%." When enrolled, the majority of these patients had poorly controlled T2DM despite having been on multi-drug therapy. When ITCA 650 was added to their regimens, 25% of these patients reached an HbA_{1c} goal of less than 7% by week 39.

The safety and efficacy of the ITCA 650 pump system compared with twice-daily exenatide injections (Ex-BID) was evaluated in a two-stage, phase II trial in patients with T2DM inadequately controlled with metformin.[63] Stage I (n=155) evaluated patient outcomes after 12 weeks of treatment with 20 or 40 mcg/day of ITCA 650 or Ex-BID. Stage II (n=131) randomly reassigned patients to receive 20, 40, 60, or 80 mcg/day of ITCA 650 for an additional 12 weeks. Henry and colleagues published the results in May 2013.[63] They reported that HbA_{1c} was significantly lower in all study groups after 12 and 24 weeks. Stage I mean change in HbA_{1c} (from a mean baseline of 7.9% to 8.0%) for the 20 and 40 mcg/day ITCA 650 and Ex-BID groups was -0.98%, -0.95%, and -0.72%, respectively. HbA_{1c} levels of 7% or less were achieved by 63%, 65%, and 50% of patients, respectively ($p<0.05$). Stage II patients had significant ($p<0.05$) reductions in HbA_{1c} (~1.4% from baseline) with 60 and 80 mcg/day ITCA 650; at 24 weeks, 86% and 78% of patients had HbA_{1c} of 7% or less; respectively. Weight reductions were also observed—a loss of 2.8 to 3.7 kg ($p<0.05$) at 24 weeks in all except the group that received 20 mcg/day in both stages of the trial. ITCA 650 was reported to be well tolerated.

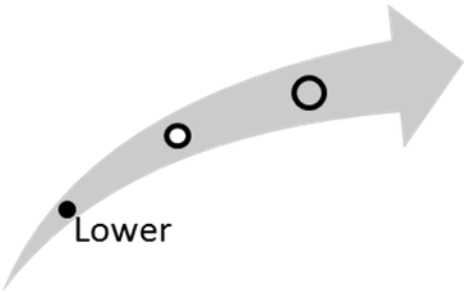
Manufacturer and regulatory status: Intarcia Therapeutics, Inc., Hayward, CA, is developing the ITCA 650 system for continuous subcutaneous delivery of exenatide. Two phase II clinical trials have been completed.[64] The FREEDOM trial is being conducted in collaboration with Quintiles, Inc., Durham, NC, a global clinical-research organization.[65] In November 2014, the company announced a partnership that grants exclusive rights to Servier (Neuilly sur Seine, France) to market the ITCA 650 system outside of the United States and Japan territories.[66] The company anticipates submitting a premarket application to FDA in early 2016.

Diffusion: ITCA 650 is most likely to compete with injected exenatide (administered once weekly) and liraglutide (administered once daily).[55,56,67] The cost for ITCA 650 has not been determined, but it will likely be priced at a slight premium to existing injectable exenatide formulations because of its novelty and convenience.[68] Although ITCA 650 use would add to the up-front cost of therapy, it could potentially save costs if it improves patient adherence to prescribed treatment, slows disease progression and development of secondary complications, and eliminates the attendant health services needed to treat those complications.

Clinical Pathway at Point of This Intervention

T2DM typically occurs in middle age or later, although incidence in a younger population has been growing as a result of the obesity epidemic. Initial treatment includes dietary modification, exercise, and self-monitoring of blood glucose. First-line drug therapies include biguanides, sulfonylureas, alpha-glucosidase inhibitors, insulin sensitizers, insulin secretagogues, and dipeptidyl peptidase-4 inhibitors. Some patients require combination drug therapy of agents with different mechanisms of action for additive therapeutic effects and better glycemic control. Despite the availability of oral antidiabetes drugs, many patients do not achieve treatment goals and require additional therapy with an injected antidiabetes agent: subcutaneous insulin or a GLP-1 agonist.[54]

Figure 2. Overall high-impact potential: ITCA 650 (exenatide continuous subcutaneous delivery) for treatment of type 2 diabetes



Overall, experts commenting on this intervention agreed on the need for effective T2DM treatments, citing patient adherence issues and the lack of efficacy of available treatments. Experts commented that this intervention has the potential to improve patient health by reducing the burden of frequent injections. Several experts expressed concerns over the potential for side effects with GLP-1 receptor agonists, including pancreatitis and pancreatic cancer, although a causal link has not been established. Experts agreed on the potential for widespread acceptance by both clinicians and patients. Patients would likely accept this intervention, especially if they are achieving adequate glucose control with available GLP-1 receptor agonists. However, one expert commented that patients may not want a device implant because it requires a slightly invasive procedure relative to oral medications. Experts generally agreed that the initial cost of the device would likely be offset by the long-term savings from reduced disease-related complications, if ITCA 650 is proved effective. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion

Six experts, with clinical, research, and health systems backgrounds, provided perspectives on ITCA 650 (subcutaneous exenatide).[69-74] We have organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: ITCA 650's subcutaneous delivery could improve patient adherence to therapy and, therefore, significantly address an unmet need, the experts generally agreed. One clinical expert stated, "Diabetes is a significant disease state where compliance with treatment has a clear impact on overall control and treatment. Although there are other GLP-1 receptor agonists available there is no other long-term depot type/or other long term delivery system available on the market. It would likely result in the highest degree of consistent treatment."[70]

This intervention has the potential to improve patient health outcomes, most experts agreed, citing the intervention's long-term glycemic control and the potential to reduce disease-related comorbidities. One expert representing a research perspective commented, "The medication, exenatide, is already an established therapy in the management of type 2 diabetes. The mode of delivery, an implanted pump, is an established therapy for other drugs or other treatments. The benefit of the pump is that it can assist patients in more consistent and accurate dosing of exenatide, and will increase patient compliance."[71] However, some experts expressed concerns about potential adverse events. One expert representing a clinical perspective opined, "As with other GLP1 drugs, there are concerns about pancreatitis, pancreatic cancer and thyroid cancer which need to be monitored over time."[69]

Acceptance and adoption: Experts agreed on the potential for widespread acceptance by both clinicians and patients. Patients would likely accept this intervention, especially if they are achieving adequate glucose control with available GLP-1 receptor agonists, the experts thought.

One expert representing a research perspective opined, "Patients are very likely to accept this course of treatment. It requires only a short in-office procedure for insertion and removal. Side effects are minimal. Unlike other treatments for T2DM, management of therapy with the ITCA 650 is controlled by the device and requires no input by the patient and no ongoing often painful procedures for administration."[73] Alternatively, one health systems expert commented that patients may not be willing to undergo device implantation due to concerns regarding continued adverse events.[72]

Health care delivery infrastructure and patient management: Experts commenting on this intervention agreed on a minimal disruption to health care delivery infrastructure, citing the straightforward method of device implantation.

Overall, patient management would likely be subject to a minimal disruption, the experts commented. According to one research expert, the addition of this intervention is not likely to cause a major disruption because of the comprehensive nature of diabetes management.[71]

Health disparities: This intervention would have a minimal potential impact on health disparities, thought the experts. Some listed cost and limited access to care as potential factors that could increase disparities. However, one research expert opined that this treatment has the potential to improve health disparities, "Patients with less access to care (socioeconomic, geographically limited) may be the best targets for this type of long delivery system as they are likely to be less amenable to the lifestyle of daily or weekly injectables."[74]

Diabetic Macular Edema Intervention

Fluocinolone Acetonide Implant (Iluvien) for Treatment of Diabetic Macular Edema

Unmet need: The standard treatment for diabetic macular edema (DME) is laser photocoagulation, and this treatment cannot reverse vision loss that has already occurred. Vision loss continues to progress in some patients despite treatment.[75-77] Additional vision loss is also a risk associated with the traditional standard of care, laser photocoagulation.[75]

Recently, intravitreal injection has become a standard treatment for DME. One such injected agent is ranibizumab, which FDA approved in 2012 for treating DME; it purportedly functions as an anti-angiogenic agent. Additionally, because inflammation is thought to play a role in DME, off-label corticosteroid injections have been used by some retinal physicians to treat DME. Both anti-angiogenic and corticosteroid treatments require ongoing treatment involving multiple intravitreal injections per year for effective treatment.[78-80] Thus, interest exists in developing more convenient and safer intravitreal therapies. An intravitreal insert that provides a sustained release of the corticosteroid fluocinolone acetonide (Iluvien®) is being developed as a potential long-term treatment for DME.

Intervention: Iluvien is a sustained-release, intravitreal corticosteroid insert intended for treating DME.[81] The insert consists of 190 mcg of the corticosteroid fluocinolone acetonide in a tiny, cylindrical, polyimide tube designed to provide sustained drug release into the eye. The insert is delivered by intravitreal injection to the back of the eye with a 25-gauge needle, a needle size that purportedly allows natural physiologic sealing of the injection site. Iluvien is designed to have a therapeutic effect for up to 36 months through stable, long-term release of fluocinolone acetonide into the eye.[81,82] In clinical trials, two doses of Iluvien were administered to patients with DME: a high dose with an initial release rate of 0.45 mcg per day or a low dose with an initial release rate of 0.23 mcg per day.[81]

Clinical trials with Iluvien have demonstrated that patients with persistent DME responded well to Iluvien treatment despite poor responses to other treatments and that patients who had had DME for 3 years or longer responded better to treatment than those who had had DME for less than 3 years.[83] The exact mechanism for this improved visual acuity after treatment in patients with longer-duration DME is not known. Investigators hypothesize that chronic edema may exacerbate the inflammation that occurs in DME and that corticosteroids exert a therapeutic effect by modulating vascular permeability via several mechanisms including inflammatory cell inhibition, inflammatory cytokine downregulation, and stabilization of cell membranes and tight junctions.[78,83]

Clinical trials: In a February 2013 analysis of two multinational trials in patients with DME previously treated with macular laser photocoagulation, authors reported that fluocinolone acetonide intravitreal implant 0.2 mcg/day was significantly more efficacious than sham injection in improving visual acuity. At 24 months after injection, 29% of recipients improved their best-corrected visual acuity (BCVA) letter score by 15 points or more compared with 16% in the sham injection group ($p=0.002$). The subgroup of patients whose DME duration was for 3 years or more achieved the greatest benefit, according to investigators. At 36 months, 34% of this subgroup increased their BCVA scores by 15 points or more compared with 13% of sham injection recipients ($p<0.001$). Fluocinolone acetonide intravitreal implant recipients also experienced generally more benefits than the control group on secondary endpoints. In patients who were phakic in the study eye at baseline, cataracts occurred in 82% of patients receiving the implant 0.2 mcg/day and 51% of sham injection recipients. Overall, 37% and 12% of patients in the fluocinolone acetonide intravitreal implant and sham injection groups developed elevated intraocular pressure (IOP), which was generally controlled with medication.[84]

Two publications[83,85] reported on the same phase III clinical trial (FAME™), which evaluated 953 patients over 36 months. We report here only the findings from the most recent (June 2012) publication.[83] At 36-month followup, 28.7% of patients receiving a low dose and 27.8% of patients receiving a high dose of fluocinolone acetonide gained 15 points or more in letter score using the last observation carried forward method, compared with 18.9% in the sham group (p=0.018). Preplanned subgroup analysis demonstrated a doubling of benefit compared with sham injections in patients who reported a DME duration of 3 years or more at baseline. The percentage who gained 15 points or more in letter score at month 36 was 34.0% (low-dose group; p<0.001) or 28.8% (high-dose group; p = 0.002) compared with 13.4% (sham group). An improvement 2 or more steps in the [ETDRS] retinopathy scale occurred in 13.7% (low-dose group) and 10.1% (high-dose group) compared with 8.9% in the sham group. Almost all phakic patients in the medication-implant groups developed cataracts, but their visual benefit after cataract surgery was similar to that in pseudophakic patients. The incidence of incisional glaucoma surgery at 36 months was 4.8% in the low-dose group and 8.1% in the high-dose insert group.

Manufacturer and regulatory status: pSivida Corp., Watertown, MA, develops minute, sustained-release, drug-delivery products designed to deliver drugs at a controlled and steady rate for months or years; it has licensed Iluvien to Alimera Sciences, Inc., Alpharetta, GA. In June 2010, after completing the FAME study, the companies submitted an NDA to FDA. In September 2014, following lengthy communication with FDA, Iluvien was granted marketing approval for treating DME in patients "who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure."[86] The approval was based on 24-month results presented by Campochiaro and colleagues.[85,87] Iluvien is being marketed in Austria, France, Germany, Italy, Portugal, Spain, and the United Kingdom for treating "DME considered insufficiently responsive to available therapies."[88,89]

Diffusion and costs: The drug is likely to compete with laser photocoagulation and off-label corticosteroid injections for DME;[78-80] these treatments cannot reverse vision loss that has already occurred, and vision loss continues to progress in some patients despite those treatments.[75-77] Additional vision loss is also a risk associated with laser photocoagulation.[75] Fluocinolone acetonide could also complement laser therapy and might be potentially more convenient and safer than corticosteroid therapy, because it would not require ongoing intravitreal steroid injections; thus, patients might find it a more appealing option.

In the United States, costs for the Iluvien implant, the procedure, and required followup visits have not been established yet because of the recency of the FDA approval. In England, the Iluvien implant is available at a discounted price of £5,500 (about $8,633 at December 2014 exchange rates).[90] The implant procedure costs £381 (about $598) and followup visits cost £240 (about $377).[91] Some industry analysts expect the product to be priced comparably to Retisert®, a fluocinolone acetonide ophthalmic implant that is FDA-approved to treat uveitis. According to ECRI Institute's PriceGuide database, the price of a single Retisert implant is about $18,250.[92] The product is designed to deliver its drug payload over 30 months.[93] Other cutting-edge ophthalmic treatments, such as pegaptanib (Macugen®) injections, which are indicated to treat wet age-related macular degeneration, cost about $8,000 to $9,000 per patient per year (approximately $1,000 per injection).[93]

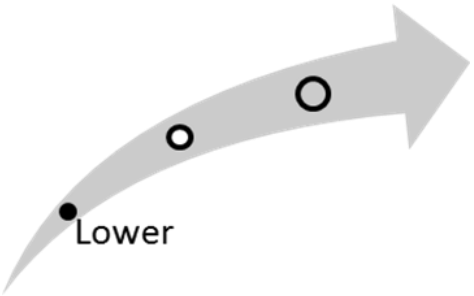
The fluocinolone acetonide implant will also probably compete with ranibizumab (Lucentis®), a vascular endothelial growth factor (VEGF) inhibitor approved for treating DME with monthly intravitreal injections.[94] According to a U.S.-based, online aggregator of prescription-drug prices, GoodRx, ranibizumab cost an estimated $2,000 per vial in December 2014 with the use of a coupon.[95]

Additional DME treatment options under investigation include other corticosteroid medications and anti-VEGF agents. Ozurdex® (formerly Posurdex) is a biodegradable intravitreal implant that releases low doses of the corticosteroid dexamethasone over 4 months.[96,97] The drug has been approved by FDA for treating DME, uveitis, and other ocular disorders.[98] Bevacizumab (Avastin®) and pegaptanib (Macugen®) are anti-VEGF (antiangiogenic) drugs typically used in cancer treatment and age-related macular degeneration; in clinical trials, researchers are testing the efficacy of small doses for treating DME.[99] In one recently completed phase IV study, researchers studied the efficacy of combining Ozurdex with bevacizumab for treating DME.[100] Bevacizumab is reportedly used widely for off-label treatment of ophthalmic conditions, including DME, as a significantly less-expensive alternative to ranibizumab.[101-104] However, some researchers report that intravitreal injections of bevacizumab are associated with a significantly higher rate of serious adverse events (because of the dose-preparation requirements for ophthalmic administration), which could pose an additional cost burden to treat. In one Canadian retrospective study, subjects who received bevacizumab for ophthalmic indications were 12 times as likely to develop severe intraocular inflammation after each injection as were patients who received ranibizumab injections.[105]

Clinical Pathway at Point of This Intervention

All patients with a diagnosis of diabetes mellitus are at risk of developing DME. A patient who presents with symptoms suggesting DME undergoes a history and physical examination pertaining to diabetes history, vision and eye-disease history, and other risk factors (i.e., older age, poor glucose control, pregnancy, hypertension, and increased lipid levels).[106] Using a high-magnification ophthalmoscope, the ophthalmologist can identify the retinal thickening that indicates macular edema. Yellow exudates and poor visual acuity may also be detected. DME treatment focuses on glycemic control, optimal blood pressure control, and macular focal/grid laser photocoagulation. Standard therapy has been laser photocoagulation and use of ranibizumab or off-label bevacizumab.[106]

Figure 3. Overall high-impact potential: fluocinolone acetonide implant (Iluvien) for treatment of diabetic macular edema



A significant unmet need exists for effective DME treatments, experts agreed. They opined that this implant has the potential to improve patient health outcomes, citing increased medication adherence. However, several experts expressed concerns regarding potential adverse events, including cataracts and increased intraocular pressure. Experts generally wanted to see more data, including comparative trials with monthly intravitreal injections of ranibizumab. Clinician acceptance is likely to be moderated by the potential for adverse events, experts thought; but patients would be more likely to accept this intervention for its convenience. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Five experts, with clinical, research, and health systems and administration backgrounds, provided perspectives on the fluocinolone acetonide implant.[107-111] We have organized the following discussion of expert comments according to the parameters on which they commented. Note: expert comments were received before FDA granted marketing approval of Iluvien for treating patients with DME.

Unmet need and health outcomes: DME is one of the leading causes of blindness, and an important unmet need exists for safe and effective therapies for patients with this condition, most of the experts agreed. However, one research expert noted that standard DME therapy is available through laser photocoagulation, corticosteroids, or anti-VEGF therapies, making this new intervention just another treatment option.[108]

Most experts commenting on this intervention questioned its potential to improve health outcomes, citing safety concerns and limited efficacy data. One research expert commented, "The one study that compared Iluvien with SOC [standard of care] reported no significant difference in efficacy at 3 years. However, IOP ≥30 mmHg was recorded in 61.4% of implanted eyes at any time and 33.8% required surgery for ocular hypertension by 4 years."[107] The same expert opined that this intervention could potentially improve patient health outcomes by improving patient adherence.[107]

Acceptance and adoption: Experts opined that clinician acceptance would likely be limited by the potential for adverse events, including cataracts and glaucoma. One research expert opined, "Clinicians will take into consideration this intervention because of the single injection vs. multiple injections of other drugs. However, the high incidence of cataracts and the absence of long-term data might cause some clinicians to not use Iluvien in young patients."[108]

Experts generally agreed that patient acceptance may be limited by the potential for adverse events, although some would be willing to accept the associated risks if this treatment proves to be effective. One health systems expert commented, "There is a greater significance of developing cataracts; however, surgeries to remove cataract are highly successful and suspect that developing cataracts will be acceptable to patients for Iluvien implants will prevent/slow down the progression of DME and blindness."[110]

Health care delivery infrastructure and patient management: Experts agreed that the fluocinolone acetonide implant would not disrupt health care delivery infrastructure, citing the potential for fewer physician-office visits. Experts did not anticipate a major impact to patient management, either. Most noted the similarities of this therapy's administration with intravitreal injections. However, some experts expressed concerns about the potential for increased physician office visits because of adverse events. One research expert opined, "Based on results of clinical trials, [it] would increase numbers of procedures performed to correct cataracts and elevated intraocular pressure (IOP)."[107]

Health disparities: Most experts agreed that this intervention would not be likely to affect health disparities. One research expert opined that the administration schedule for the fluocinolone acetonide implant could potentially provide better access to treatment for some patients compared with DME therapies that require more frequent intravitreal injections (e.g., anti-VEGF therapies).[108] This expert also thought that the cost of the implant could limit access to certain populations: "If priced similar to Retisert ($18,250), it might be an option only for those with high economic status and/or those with access to health insurance that grant coverage."[108]

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